Atty. Dkt. No. 029488-0111

DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I HEREBY DECLARE:

THAT my residence, post office address, and citizenship are as stated below next to my name;

THAT I believe I am the original, first, and sole inventor (if only one inventor is named below) or an original, first, and joint inventor (if plural inventors are named below or in an attached Declaration) of the subject matter which is claimed and for which a patent is sought on the invention entitled

TREATMENT OF MASTALGIA WITH 4-HYDROXY TAMOXIFEN

(Attorney Docket No. 029488-0111)

the specification of which (check one)

___ is attached hereto.

__X__ was filed on December 15, 2003 as United States Application Number or PCT International Application Number 10/734,640 and was amended on _____ (if applicable).

THAT I do not know and do not believe that the same invention was ever known or used by others in the United States of America, or was patented or described in any printed publication in any country, before I (we) invented it;

THAT I do not know and do not believe that the same invention was patented or described in any printed publication in any country, or in public use or on sale in the United States of America, for more than one year prior to the filing date of this United States application;

THAT I do not know and do not believe that the same invention was first patented or made the subject of an inventor's certificate that issued in any country foreign to the United States of America before the filing date of this United States application if the foreign application was filed by me (us), or by my (our) legal representatives or assigns, more than twelve months (six months for design patents) prior to the filing date of this United States application;

THAT I have reviewed and understand the contents of the above-identified specification, including the claim(s), as amended by any amendment specifically referred to above;

THAT I believe that the above-identified specification contains a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with

which it is most nearly connected, to make and use the invention, and sets forth the best mode contemplated by me of carrying out the invention; and

THAT I acknowledge the duty to disclose to the U.S. Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

I HEREBY CLAIM foreign priority benefits under Title 35, United States Code §119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or §365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below any foreign application for patent or inventor's certificate or of any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number	Country	Foreign Filing Date	Priority Claimed?	Certified Copy Attached?

I HEREBY CLAIM the benefit under Title 35, United States Code § 119(e) of any United States provisional application(s) listed below.

U.S. Provisional Application Number	Filing Date
60/433,959	12/18/2002

I HEREBY CLAIM the benefit under Title 35, United States Code, §120 of any United States application(s), or § 365(c) of any PCT international application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of Title 35, United States Code, § 112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

U.S. Parent Application Number	PCT Parent Application Number	Parent Filing Date	Parent Patent Number

S. Ryan

I HEREBY APPOINT the registered attorneys and agents at Customer Number 22428

Customer Number: 22428

to have full power to prosecute this application and any continuations, divisions, reissues, and reexaminations thereof, to receive the patent, and to transact all business in the United States Patent and Trademark Office connected therewith.

I request that all correspondence be directed to:

Stephen A. Bent
FOLEY & LARDNER
Customer Number: 22428

Telephone: (202) 672-5404
Facsimile: (202) 672-5399

I UNDERSTAND AND AGREE THAT the foregoing attorneys and agents appointed by me to prosecute this application do not personally represent me or my legal interests, but instead represent the interests of the legal owner(s) of the invention described in this application.

I FURTHER DECLARE THAT all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Name of first inventor	Bruno de Lignières
Residence	Draveil
Citizenship	France
Post Office Address	34, rue des Claudines 91210 Draveil
Inventor's signature	G. Lignières Gabrielle Elisabeth Brink de Lignières as legal representative for Bruno de Lignières Mme Gabrielle Elisabeth de Lignieres Residence: Draveil, France Post Office Address: 34 rue des Claudines 91210 DRAVEIL France Citizenship: France
Date	04. June-2007

Atty. Dkt. No. 029488-0111

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Bruno DE LIGNIERES

Title: **TREATMENT OF MASTALGIA WITH 4-HYDROXY TAMOXIFEN**

Appl. No.: 10/734,640

Filing Date: 12/15/2003

Examiner: U. Ramachandran

Art Unit: 1617

Confirmation Number: 9061

DECLARATION OF JEAN L. FOURCROY, M.D. UNDER 37 C.F.R. § 1.132

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Jean L. Fourcroy, M.D., do hereby declare and state as follows:

1. I received an M.D. degree from the Medical College of Pennsylvania in 1974, a Ph.D. from the University of California at San Francisco in 1977, and a Masters in Public Health from the Medical College of Wisconsin in 1999. I completed surgery and urology residencies at George Washington University Medical Center and earned Board Certification in Urology in 1981. I was a Medical Officer with the Food and Drug Administration for almost 20 years. In this capacity I was involved with many aspects of the regulatory process, including the development of new drugs, devices and issues surrounding supplements. My research has included a wide range of developmental and reproductive biology. I am currently a regulatory consultant in areas of urology and endocrinology. I have been appointed to the Board of the U.S. Anti-Doping Agency and am an active member of the American Urological Association, the American Society of Andrology, and Past President of the American

Medical Women's Association. I serve on the editorial board of NCI/PDQ Prevention and Screening. My CV is attached.

2. From time to time I have been retained by Ascend Therapeutics, Inc. as a consultant to provide my professional opinion on various matters. Ascend Therapeutics, Inc. has retained me to prepare this Declaration, for which I am being compensated for my time at my usual consulting rate of $300/hour.

3. I understand that Ascend Therapeutics, Inc. is the licensee of U.S. Patent Application 10/734,640 ("the application"), which I have reviewed and which I understand is directed to treating mastalgia using 4-hydroxy tamoxifen.

4. I have reviewed the Office Action mailed March 12, 2007, where the Patent Office Examiner states that the method described in the application is obvious in view of (i) Fentiman *et al.*, *Br. J. Surg.* 75: 845-46 (1988); (ii) Pujol *et al.*, *Cancer Chemother. Pharmacol.* 36: 493-98 (1996); (iii) Kochinke, U.S. Patent 5,613,958; (iv) Mauvais-Jarvis *et al.*, *Cancer Res.* 46: 1521-25 (1986); and (v) Malet et al., *Cancer Res.* 48: 7193-99 (1988).

5. I provide the following statements on this issue, which I understand may be used to support the application. The opinions expressed here are based on my knowledge and experience in the field.

6. I understand the Patent Office Examiner's position to be based on the following: (i) Fentiman describes the use of tamoxifen to treat mastalgia, (ii) Pujol (and other publications) mentions that 4-hydroxy tamoxifen is an active metabolite of tamoxifen, and (iii) Pujol describes the transdermal administration of 4-hydroxy tamoxifen to breast cancer patients. Apparently, the Patent Office Examiner believes that, because 4-hydroxy tamoxifen is an active metabolite of tamoxifen, it would have been obvious to use 4-hydroxy tamoxifen to treat conditions that have been treated with tamoxifen, such as in the Fentiman method to treat mastalgia. I must disagree.

7. The Fentiman paper describing the use of tamoxifen for the treatment of mastalgia does not refer in any way to the percutanous use of 4-hydroxy tamoxifen for the

treatment of mastalgia. While the Pujol paper reports the administration of 4-hydroxy tamoxifen to breast cancer patients, it does not show the treatment of mastalgia, which is not a cancerous breast condition. Moreover, it is not possible to extrapolate from Fentiman's use of tamoxifen to the use of 4-hydroxy tamoxifen described in the application, or from Pujol's administration to breast cancer patients to the treatment of mastalgia.

8. It is important to understand that tamoxifen and 4-hydroxy tamoxifen are distinct agents, each with unique safety and efficacy profiles. For example, tamoxifen manifests different biological activities in different cells. It is dependent upon cytochrome P450 enzymes for metabolism to a more active metabolite, such as 4-hydroxy-tamoxifen, and it is a potent rat liver carcinogen, unlike 4-hydroxy tamoxifen. *See, e.g.*, Carthew *et al.*, *Archives of Toxicology* 75: 375-80 (2001); Sauvez *et al.*, *Carcinogenesis* 20: 843-50 (1999).

9. For both tamoxifen and 4-hydroxy tamoxifen, the final response element at the cellular level is dependent on the unique conformation of the estrogen receptor in the individual cell type. *See, e.g.*, Wijayaratne *et al.*, *Endocrinology* 140: 5828-840 (1999); Giambiagi *et al.*, *J. Steroid Biochem.* 30: 213-17 (1988). Estrogen receptor binding by tamoxifen recruits different co-factors than estrogen receptor binding by 4-hydroxy tamoxifen. For example, tamoxifen initiates apoptosis in p53(-) normal human mammary epithelial cells, while 4-hydroxy tamoxifen does not. *See, e.g.*, Dietze *et al.*, *J. Biological Chemistry* 276: 5384-394 (2001). On the other hand, 4-hydroxy tamoxifen inhibits estrone sulphatase activity in mammary cancer cell lines, while tamoxifen has little effect in this regard. *See, e.g.*, Chetrite *et al.*, *Anticancer Research* 13: 931-34 (1993).

10. The literature illustrated by the publications that I have cited above demonstrate that tamoxifen and 4-hydroxy tamoxifen have different modes of action. Thus, persons versed in this field understand that knowing that tamoxifen is useful in a given therapeutic regimen does not provide a reasonable basis for expecting that 4-hydroxy tamoxifen would be useful for the same purpose.

11. I also understand the present invention to provide significant advantages over the state of the art, particularly over the use of tamoxifen to treat mastalgia. This is because percutaneous 4-hydroxy tamoxifen offers important safety improvements for the treatment of this prevalent women's health disease. While the side effects of tamoxifen were known, it was not known that 4-hydroxy tamoxifen would be useful to treat mastalgia. Thus, the application describes a significant advance in the treatment of mastalgia.

12. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful, false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that willful, false statements may jeopardize the validity of the application or any patent issued thereon.

6-10-07
DATE

Jean L. Fourcroy, M.D.